Remarks

Claims

The claims were not amended with this response. A list of the pending claims are provided.

Priority

The Office accords the instant application a priority date of December 2, 2003, which is the filing date of the application. The Office did not accord the instant application the benefit of the earlier priority applications because it alleges that while U.S. Provisional application 60/334,461 contains support for the terms "RNA interference" or "RNAi" and also contains support for GenBank Accession Number NM_002019 (page 55), it does not have support for SEQ ID NO: 14 recited in the claims. Specifically, the Office alleges that GenBank Accession Number NM_002019 and SEQ ID NO: 14 are not the same sequence because SEQ ID NO: 14 contains uracil residues and GenBank Accession Number NM_002019 contains thymine residues.

The Office contends that because SEQ ID NO:14 and GenBank Accession Number NM_002019 are not the same sequence, U.S. Provisional application 60/334,461 does not provide sufficient support for the claims (which recite SEQ ID NO: 14). Contrary to the Office's contention, Applicant submits that U.S. Provisional application 60/334,461 provides sufficient disclosure to support a priority claim.

First, U.S. Provisional application 60/334,461 teaches GenBank Accession Number NM_002019 on page 55. A review of the GenBank database shows the following information for GenBank Accession No. NM_002019:

```
LOCUS       NM_002019              7680 bp    mRNA    linear   PRI 31-OCT-2000
DEFINITION  Homo sapiens fms-related tyrosine kinase 1 (vascular endothelial
            growth factor/vascular permeability factor receptor) (FLT1), mRNA.
ACCESSION   NM_002019
VERSION     NM_002019.1  GI:4503748
KEYWORDS    .
SOURCE      Homo sapiens (human)
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Applicant notes that GenBank Accession No. NM_002019 is identified as an "mRNA" sequence having 7680 nucleotides. One skilled in the art would know that the corresponding mRNA sequence of the gene sequence has uracil residues rather than thymine residues. It is certainly within the skill of the ordinary artisan to take the exact same nucleotide sequence and merely replace the thymine residues with uracil residues.

For the reasons provided, applicant submits that U.S. Provisional application 60/334,461 provides sufficient descriptive support and that the instant application should be afforded the November 30, 2001 priority date (the filing date of U.S. Provisional application 60/334,461).

Objection to the Specification

The Office objects to the amendment filed on September 20, 2006 because it allegedly introduces new matter into the specification. Specifically, the Office alleges that the sequence listing filed with the September 20, 2006 amendment added SEQ ID NO:14, which sequence appears to be new matter. SEQ ID NO: 14 represents GenBank NM_002019, which GenBank number is disclosed in the instant specification. However, the Office contends that the addition of SEQ ID NO: 14 in the September 20, 2006 sequence listing adds new matter because GenBank NM_002019 contains thymine residues, where SEQ ID NO:14 has replaced all of the thymine residues with uracil residues. The Office concludes that the replacement of all thymine nucleotides of GenBank NM_002019 with uracil nucleotides in SEQ ID NO:14 represents new matter.

The Applicants respectfully submit that SEQ ID NO:14 is not new matter for the reasons set forth herein below. Accordingly, Applicants should not be required to cancel the addition of SEQ ID NO:14 to the sequence listing.

35 USC §112, First Paragraph, Rejections

Written Description/New Matter

Claims 1-8 and 10-26 have been rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Office argues that the addition of SEQ ID NO:14, which was added to the sequence listing filed on September 20, 2006, adds new matter because SEQ ID NO:14 and GenBank Accession Number NM_002019 are not the same sequence. Specifically, the Office argues that the replacement of thymine residues with uracil residues in SEQ ID NO:14 adds new matter.

Applicant respectfully disagrees. The application teaches throughout the specification that the siRNA molecules are complementary to and target VEGFr RNA sequences. Table II includes sequences targeted to GenBank Accession No. NM_002019. Thus, the specification clearly

contemplates nucleic acid molecules comprising nucleotides that are complementary to VEGFr **RNA** nucleotide sequence comprising SEQ ID NO:14.

Furthermore, a review of the GenBank database shows the following information for GenBank Accession No. NM_002019:

```
LOCUS       NM_002019               7680 bp    mRNA    linear   PRI 31-OCT-2000
DEFINITION  Homo sapiens fms-related tyrosine kinase 1 (vascular endothelial
            growth factor/vascular permeability factor receptor) (FLT1), mRNA.
ACCESSION   NM_002019
VERSION     NM_002019.1  GI:4503748
KEYWORDS    .
SOURCE      Homo sapiens (human)
```

Applicants note that GenBank Accession No. NM_002019 is identified as an "mRNA" sequence having 7680 nucleotides. Accordingly, one of ordinary skill in the art would have known that the RNA sequence is the same as the reported sequence, except with uracils substituted for thymines. Such substitution would have easily been within the knowledge and skill of the ordinary skilled artisan.

One of skill in the art would have understood that the applicants were in possession of the invention at the time the application was filed. Therefore, the claims have adequate written description. Applicants respectfully request withdrawal of the rejection.

Enablement

Claims 1-8 and 10-26 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to describe the claimed subject matter in such a way as to enable one skilled in the art to make and/or use the invention. The Applicant respectfully traverses the rejection.

The specification as filed fully enables the claimed invention. The *Wands* factors typically considered by the Office in formulating the enablement rejection include the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary. All the applicant is required to show is that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The showing provided by the applicant need not be conclusive but merely convincing to one skilled in the art (see MPEP 2164.05).

Under 35 U.S.C. §112, all that is required for satisfaction of the enablement requirement is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *US v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); M.P.E.P. §2164.01. The contours of the "undue experimentation" standard have been outlined in several cases. The Federal Circuit has explained that "[t]he key word is 'undue' and not 'experimentation'. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); see also *Massachusetts Institute of Technology vs. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The Office argues that while the specification is enabling for a method of locally administering to a cell or tissue *in vitro* a double stranded RNA complementary to a nucleotide sequence of a VEGF receptor, it does not reasonably provide enablement for a method of locally administering to a cell or tissue *in vivo* (whole organism). Contrary to the Office's position that *in vivo* administration is not enabled, Applicant submits that the instant specification teaches appropriate methods of administration to cell and animal models and provides data that is reasonably predictive of administration *in vivo*. As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate* (emphasis added)." MPEP 2164.02; *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The various models taught in the specification are appropriate models that one skilled in the art would consider to be reasonably predictive of administration *in vivo*. Thus, the described efficacy of double stranded nucleic acid molecules in an appropriate cell culture or animal model would have been readily accepted by a person skilled in the art to be reasonably predictive of the ability of these molecules to cleave target VEGFr1 sequences in cells and *in vivo*, and thereby be effective in an *in vivo* application. As further support for this position, the Federal Circuit has found that data showing the successful use of compounds as

antitumor substances in tumor model systems were sufficient to enable the use of those compounds as anticancer drugs in animals. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

Furthermore, the specification teaches one skilled in the art how to make and use the double stranded nucleic acid for *in vivo* administration. The specification teaches one how to design (see for example pages 33-34), synthesize (see for example pages 34-38), and administer (see for example pages 46-55) double stranded nucleic acids that target VEGFR1. Furthermore, the specification teaches how to evaluate such double stranded nucleic acid molecules using *in vivo* animal models of angiogenesis (see for example pages 61-62 and U.S. Provisional Patent application NO. 60/393,796 at page 68, line 20 to page 75, line 14). The specification teaches that the double-stranded nucleic acids can be used to down regulate gene expression (page 33, lines 14-26) and also provides supporting evidence that inhibition of VEGFR1 expression using double stranded nucleic acids as claimed results in significant inhibition of angiogenesis *in vivo* (see for example pages 1-5 and 59-61 and U.S. Provisional Patent application NO. 60/393,796 at page 68, line 20 to page 75, line 14). Thus, the specification enables one of skill in the art to practice the claimed invention by describing how to design, synthesize, administer, and test double stranded nucleic acid molecules targeting VEGFR1 in vivo by providing specific examples of such double stranded nucleic acid molecules, and by demonstrating that the double stranded nucleic acid molecules inhibit angiogenesis.

As discussed above, the specification teaches methods of locally administering double stranded RNA molecules to a tissue or cell using appropriate models that are reasonably predictive of *in vivo* administration. Furthermore, using the teachings provided in the instant application, Applicant has actually shown that local administration of double stranded nucleic acid molecules targeting VEGFR1 gene expression can be used to inhibit angiogenesis *in vivo*. In U.S. Provisional Patent Application No. 60/393,796 at page 72, line 7 to page 75, line 14, which is incorporated by reference in the instant application, Applicant has demonstrated inhibition of angiogenesis as is presently claimed using a mouse model of ocular angiogenesis (data is shown in Figure 3). Also, in co-pending US Patent Application Nos.: 11/299,391, 10/844,076, and 10/962,898, Applicant demonstrates inhibition of ocular angiogenesis using double stranded nucleic acid molecules targeting VEGFR1 RNA *in vitro* and *in vivo*. As described in USSN 10/844,076 (published as US-2005-0171039-A1) and USSN 10/962,898 (published as US-2005-0222066), Applicant designed, synthesized, and tested several double stranded nucleic acid sequences that were evaluated for efficacy in cell culture and animal models.

As described in USSN 11/299,391, applicant describes Phase I clinical trial results obtained using Sirna-027, which is a modified siRNA molecule targeting VEGFR1 RNA. Sirna-027 is a modified siRNA in development as a potential therapeutic for the pathological neovascularization common to ocular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. Sirna-027 is directed against vascular endothelial growth factor receptor 1 mRNA. VEGFR1 is the receptor in the VEGF pathway that can bind both VEGF and placental growth factor. Sirna-027 was efficacious in a mouse model of laser-induced choroidal neovascularization and in mice with ischemic retinopathy. Intravitreal or periocular injections of Sirna-027 resulted in significant reductions in ocular neovascularization in both mouse models, ranging from 32 to 66%, compared to treatment of the fellow eye with an inverted control siRNA (see co-pending application USSN 10/962,898, Example 10, pages 209-220). Ocular levels of VEGFR1 mRNA and protein were also reduced significantly. The methods and results were published in Shen *et al.,* 2005, *Gene Therapy*, 1-10. The safety, tolerability, clinical and biological activity of Sirna-027 was evaluated in an open-label, dose escalation Phase I trial in 25 patients with active choroidal neovascularization secondary to AMD. Single intravitreal injections of Sirna-027 (100 to 1200 μg) were safe and well tolerated. No ocular or systemic dose-limiting toxicities were observed. Eight weeks after the injection, all patients had stable or improved visual acuity. Reduction of central foveal thickness was observed by ocular coherence tomography in the majority of patients, suggesting biological activity of siRNA in a human (see co-pending application USSN 11/299,391, Example 9, pages 226-242).

Despite the teachings, the Office alleges that the claims are not enabled due to the unpredictability in the art. However, Applicant points out that experimentation, even a considerable amount of experimentation, is permissible, if it is merely routine. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed Cir. 1985); MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

Furthermore, the Federal Circuit has found that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Using the methods known in the art and described in the instant application, a skilled artisan could easily formulate and

test double stranded nucleic acids *in vitro* and *in vivo* as a matter of routine experimentation. The fact that modified double stranded nucleic acids are being tested in clinical trials is further evidence that the amount of experimentation necessary to practice the invention is not undue.

Finally, Applicant points out that the Office fails to provide any evidence whatsoever that the instant invention would not work for its intended purpose, other than alleging that siRNA technology is an unpredictable art. However, Applicant has provided ample data and guidance in the specification that demonstrate the efficacy of modified double stranded nucleic acid molecules. Accordingly, there is no reason to believe and the Office has not demonstrated that the claimed methods using a double stranded nucleic acid molecule to cleave VEGFr1 RNA would not have activity *in vivo*. In the absence of any technical reasons to support its reasoning, the Office has failed to establish a *prima facie* case of lack of enablement. M.P.E.P. § 2164.04.

Thus, employing the teachings in the instant application, Applicant has demonstrated a method of locally administering a double stranded RNA to a tissue or cell in vivo. Thus, the claims are enabled across the scope of the claims. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. §112 rejection.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Dated: June 11, 2007

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